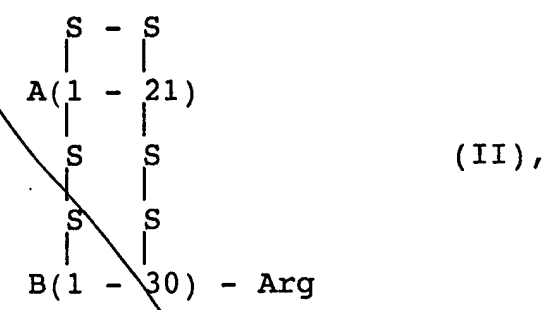
15. A method for the preparation of the compound of formula II



(II),

in which A(1-21) and B(1-30) denote the A and B chain of human insulin and the -S-S- bridges are positioned as in insulin, using the compound of formula I, as claimed in claim 1, which comprises a) expressing a DNA molecule encoding the compound of formula I in yeast; and b) cleaving said expressed compound with trypsin.--

B2 wrd.

REMARKS

Claim 11 has been cancelled, new claims 14 and 15 have been added, and claims 12-13 have been amended. Therefore, claims 1, 10, and 12-15 are pending in the application.

At page 2 of the Office Action, the Examiner states that "[a]pplicant's arguments with respect to claims 1-10 have been considered but are deemed to be moot in view of the new grounds of rejection." Therefore, it is presumed that previous grounds for rejection of claims 1-10, made in the previous Office Actions, are now withdrawn.

The Examiner rejected claims 1 and 11-13 under 35 U.S.C. § 103 as being unpatentable over either Markussen et al. (U.S. Patent No. 4,916,212) or Markussen et al. (EPO 163,529)

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for the reasons set forth at pages 3-4 of the present Office Action. Applicants respectfully traverse this rejection.

At pages 3-4, the Examiner states that

> the differences between the specific embodiment of the prior art and applicant's composition [are] the amino acid Ser instead of Thr at position 30 and Lys for Arg. The claimed generic formula of the prior art encompasses applicant's claimed composition. The different amino acids selected by applicant for these positions are preferred embodiments in the prior art.

Markussen et al. does not specifically show the particular amino acid sequence of the presently claimed compound, and the Examiner has failed to explain why she considers that the presently claimed amino acid sequence is a "preferred embodiment" of Markussen et al. How can a species that is not specifically disclosed possibly be considered a preferred embodiment of a generic formula?

In the first complete paragraph at page 4 of the Office Action, the Examiner states that

> [i]t would have been obvious to take the DNA sequence of Markussen et al. and encode Thr at amino acid position 30 and Arg instead of Lys. Both of these changes are conservative amino acid substitutions; both of these changes are to the amino acids found in human insulin; and both of these changes are preferred choices disclosed by applicant[1/]. It would have been obvious to take the resulting DNA and express it in yeast to form the composition of claim 1. There would have been a high expectation of success based on successful

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1/ It is not completely clear if the Examiner is using applicants' "preferred choices disclosed by applicant" as a basis for the obviousness rejection. However, if the Examiner is using applicants' disclosure for a basis for the obviousness rejection, such a basis is improper.

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> recombinant production of the B(1-29)-Ser-Lys-A(1-21) variant in the prior art. The methods of preparation of mono-Arg insulin or insulin (claims 11-13) as recited would have been obvious over those taught by Markussen et al. It is noted that no method steps are recited in these claims.

The correct legal standard for a successful combination of references when making a § 103 rejection is that the Examiner carries the burden of showing

> (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 U.S.P.Q. 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure. Id. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

The claimed invention has the great advantage, described at pages 2 and 3 of the present specification, that the compound of formula I can be converted to insulin in a surprisingly simple "one-pot reaction." Not only Markussen et al. do not teach the use of their compound for arriving at such an advantageous result, they fail to suggest it. In fact, applicants have informed the undersigned that certain of the numerous embodiments within the scope of Markussen et al. do not work advantageously according to the presently claimed process.

Moreover, considering that the general formula of Markussen et al. encompasses a large number of species, the Examiner has failed to establish why she considers that it would have been a routine choice for one of ordinary skill in the art to select the presently claimed species out of the vast number of

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species encompassed by the general formula of Markussen et al., and make the changes, suggested by the Examiner, to arrive at the present invention. Furthermore, the Examiner has not established with evidence or reasoning why she considers that one skilled in the art would have had a reasonable expectation of success in obtaining a proinsulin compound which is successfully and advantageously converted to insulin in a "one-pot reaction", by taking the formula of Markussen et al. and encoding Thr at amino acid position 30 and Arg instead of Lys. Moreover, Markussen et al.'s most preferred compounds, i.e., B(1-29)-Ser-Lys-A(1-21) and B(1-29)-Ala-Ala-Lys-A(1-21) (see lines 16-18 of column 3 of Markussen U.S. Patent No. 4,916,212), have a B chain with only 29 amino acids. Thus, applicants' compound containing a B chain of human insulin with 30 amino acids is certainly not "preferred" according to Markussen et al., and the Examiner has failed to present any reasons or evidence why she considers that one of ordinary skill in the art would have been motivated to modify Markussen et al. to include a B chain of 30 amino acids.

In light of the above remarks, it is clear that a prima facie case of obviousness has not been established. Therefore, the applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103.

The Examiner rejected claim 10, under 35 U.S.C. § 103 over Markussen et al. (EPO 163,529) or Markussen et al. (U.S. Patent No. 4,916,212) in view of Goeddel et al. (EPO 055,945) for the reasons set forth at pages 4-5 of the present Office Action. Applicants respectfully traverse this rejection.

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Applicants reiterate the above remarks with regard to the cited Markussen et al. references. Goeddel et al. relates to a method of preparing certain human proinsulin and its analogs by microbial polypeptide expression. Goeddel et al. does not cure the deficiencies of the primary references of Markussen et al. discussed above. Therefore, a prima facie case of obviousness has not been established, and applicants request that this rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

The Examiner rejected claims 10, 11, and 13 under 35 U.S.C. § 112, first paragraph, for the reasons set forth at pages 5-6 of the Office Action. Applicants respectfully traverse this rejection. The Examiner's arguments are addressed one as follows. Please note that claim 11 has been cancelled and new claims 14-15 have been added.

1) At lines 13-23 at page 5 of the Office Action, the Examiner states that

> [t]he specification discloses methods of preparing mono-Arg insulin, represented by formula II, from miniproinsulin, represented by formula I. However, this conversion cannot always be performed in a single vessel. The specification discloses a single reaction for the conversion of miniproinsulin produced in yeast to mono-Arg insulin (treating with trypsin). The specification discloses two separate reactions for the conversion of miniproinsulin produced in E. coli to mono-Arg insulin (denaturing with urea and renaturing which is followed by column purification, treatment of the eluted material with trypsin, see pages 14 and 15 of specification.)

Applicants respectfully assert that only the old dependent claim 13 recited carrying out all of the chemical reactions in one vessel. Claim 13 has now been amended to depend from claim 12, and it no longer includes the language which is objected to by the

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Examiner. Independent claim 12, however, does not state that the conversion of the compound of formula I to human insulin must be always performed in a single vessel.

2) At the sentence bridging pages 5 and 6 of the Office Action, the Examiner states that "[i]t is noted that formula I, B(1-30)-Arg-A(1-21), does not specify the positioning of the disulfide bonds in this single chain peptide as being positioned as in insulin."

The compound of formula I comprises amino acids 1-30 of the B chain of human insulin connected via an Arg residue to amino acids 1-21 of the A chain of the human insulin. It is not clear whether and why the Examiner considers it a requirement under Section 112, first paragraph that applicants specify the positioning of the disulfide bonds in the claimed compound of formula I. Unless the Examiner sets forth reasons or evidence why such a request is necessary under Section 112, first paragraph, applicants submit that a prima facie case has not been established based on this ground of rejection.

3) At lines 1-3 of page 6 of the Office Action, the Examiner contends that "[a]pplicant has not enabled the breadth of the claims as the source of the miniproinsulin is not a limitation of the claims."

The fusion protein of claim 10 contains, and the methods of claims 12-15 use the miniproinsulin of the formula I, as claimed in claim 1. The specification enables making of the miniproinsulin of formula I, as claimed in claim 1; for example, see Examples 2-3 wherein construction of the miniproinsulin gene

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and its expression in E. coli is disclosed. It is not clear what exactly is the limitation as to the source of the miniproinsulin which the Examiner is requiring under 35 U.S.C. § 112, first paragraph, the applicants to specify in the claims, and why. Applicants respectfully submit that the correct standard for a non-enablement rejection under 35 U.S.C. § 112, first paragraph is that a specification is presumed to be enabling; and the Examiner bears the burden of presenting evidence or reasons establishing a prime facie case why she considers that one skilled in the art would require undue experimentation to make and use the claimed invention. The Examiner has failed to establish why what she considers a required limitation of the claims as to the source of the miniproinsulin, allegedly left out by the applicants, relates to an enablement requirement under 35 U.S.C. § 112, first paragraph, as discussed above. In the absence of evidence or reasons supporting the Examiner's assertion, it is submitted that based on this ground of rejection, a prima facie case has not been established.

4) At the first complete paragraph at page 6 of the Office Action, the Examiner contends that

> [t]he specification enables an N-terminal fusion protein of IL-2 bonded via the linker Met-Ile-Glu-Gly-Arg to miniproinsulin. This fusion can be cleaved by cyanogen bromide. There is no evidence of record that IL-2 could be fused to the C-terminal of miniproinsulin. There is no description in the specification of a C-terminal fusion. Furthermore, there is no evidence in the prior art [or -sic.] of record that a C-terminal fusion to insulin, proinsulin, preproinsulin, or the A- or B-chains of insulin (when expressed individually) protects or stabilizes the insulin or precursor form from degradation in bacteria. It

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appears that all successful fusion proteins have been at the N-terminal.

As described above, for a proper non-enablement rejection under 35 U.S.C. § 112, first paragraph, the Examiner has the primary burden of establishing that undue experimentation would be required to make and use the claimed invention. Conclusions alone, without supporting evidence or reasoning are not sufficient to establish a prima facie case. Here, the Examiner has not met her burden of showing that IL-2 cannot be fused to the C-terminal of miniproinsulin. Instead, she has implied that unless the applicants provide data to specifically show that this embodiment of the invention is operative, that embodiment is considered to be inoperative by the Examiner. Applicants request that the Examiner provide evidence and/or sound scientific arguments to support her challenge to the credibility of applicants' disclosure of the invention.

Moreover, applicants assert that the C-terminal fusion of IL-2 to insulin can be carried out the same way as described in Examples 3, 4, and 5 of the specification. After expression of a gene structure coding for said fusion protein the compound is cleaved with cyanogen bromide producing the S-sulfonate of the mini-proinsulin which is subsequently cleaved with trypsin and carboxypeptidase to produce human insulin. Therefore, this specific embodiment of the invention is enabled in the specification.

In light of the above remarks, applicants respectfully request the reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

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The Examiner rejected claims 11-13 under 35 U.S.C. § 112, second paragraph for the reasons set forth at pages 6-7 of the Office Action. Applicants respectfully traverse this rejection.

At the paragraph bridging pages 6-7 of the Office Action, the Examiner states that

> [c]laims 11-13 are indefinite for failing to recite any steps that comprise the method being claimed. The claims fail to recite the steps that convert miniproinsulin to mono-Arg insulin (claims 11 and 13) or insulin (claim 12). Claim 13 is drawn to the method of claim 11 "wherein all of the chemical reactions are carried out...". However, these chemical reactions lack antecedent basis in claim 11, and furthermore, the intended chemical reactions are not specified in claim 13.

Applicants have cancelled claim 11 and added new claims 14 and 15. Support for new claims 14 and 15 is found in the present specification, e.g., at Examples 3-4 and 8-9, respectively. Claim 12 has been amended to recite the steps for the preparation of insulin by using the compound of claim 1. Support for this amendment is found in the specification, for example, in Example 10 (original Example 6). Claim 13 has been amended to delete the language "wherein all of the chemical reactions are carried out," objected to by the Examiner, and has been amended to depend on claim 12. Support for this amendment is found in the specification, for example, at page 5, lines 9-12 and Example 10 (original Example 6). In light of these amendments, applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

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In view of the foregoing amendments and remarks, it is believed that the pending claims are now in condition for allowance. Applicants respectfully request issuance of a favorable action.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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Dated: December 2, 1992

By: Raz Fleshner
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